Managing diabetes in people with severe mental illness

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Annual Conference
Exeter 28 February 2013

Duality of Interest: I have received fees for lecturing, consultancy work and attendance at conferences from the following companies: Eli Lilly & Co, AstraZeneca, BMS, Otsuka, GlaxoSmithKline, MSD
Physical Consequences of Severe Mental Illness

- Overall standardised mortality ratio (SMR) ↑ 2.5-3x
- Life expectancy is reduced by 10-20 years
- 75% of patients die from natural causes
  - 33-60% die from CVD

Osby Arch Gen Psychiatry. 2001 Sep;58(9):844-50
Overview

• Burden of diabetes

• Clinical Implications
  – Screening for diabetes
  – Preventing diabetes
  – Managing diabetes
Diabetes and severe mental illness
“Diabetes is a disease which often shows itself in families in which insanity prevails.”

Henry Maudsley (1835–1918)
Schizophrenia and Diabetes

• Precise prevalence rates unclear
  – Changing rates in general population
  – High prevalence of undiagnosed disease
    • As many as 70% may be undiagnosed
  – Reluctance for people with schizophrenia to participate in epidemiological studies
    • Screening bias

Diabetes & Schizophrenia

Percentage with Diabetes

Typical Antipsychotics
Atypical Antipsychotics
US general population

Medical Co-morbidity in Bipolar disorder

- Hypertension
- Dyslipidaemia
- Diabetes
- IHD
- COPD

Diabetes 2-3x commoner than the general population

Consequences of diabetes in people with severe mental illness

• 74% more likely to develop acute complications
• More likely to develop chronic microvascular complications
• 2-3 more likely to develop cardiovascular disease
• 6.14x more likely to die from DM

Overview

• Burden of diabetes

• Clinical Implications
  – Screening for diabetes
  – Preventing diabetes
  – Managing diabetes
Screening for Diabetes
The imperative for screening

- Glucose
- Onset of Diabetes
- Cardiovascular complications
- Microvascular complications
- Onset of symptoms

Time

10 years
Screening for Diabetes

Glucose (Fasting or Random)
Glycated Haemoglobin (HbA$_{1c}$)

Baseline (before initiating or switching treatment)
After 3-4 months
Then annually
Figure 1: Identifying and managing risk of type 2 diabetes

Stage 1

- People with SMI

- People aged 25–39 years of South Asian, Chinese, African-Caribbean, black African and other high-risk black and minority ethnic groups
- People with conditions that increase the risk of type 2 diabetes
- Use risk-assessment tools and questionnaires
- Follow NHS Health Check process and protocols where possible

Low or intermediate risk score

- Offer brief advice on:
  - The risks of developing diabetes
  - The benefits of a healthy lifestyle
  - Modifying risk factors

High risk score

- Offer a blood test
- Choose either FPG or Hba1c—use as appropriate and according to national quality specifications
- Reassess risk at least every 5 years

Stage 2

- Moderate risk
- FPG < 5.5 mmol/l or Hba1c < 42 mmol/mol (6.0%)
- Discuss the risks of developing diabetes
- Help modify individual risk factors
- Offer tailored support services

- High risk
- FPG 5.5–6.9 mmol/l or Hba1c = 42–47 mmol/mol (6.0–6.4%)
- Offer an intensive lifestyle-change programme to:
  - Increase physical activity
  - Achieve and maintain weight loss
  - Increase dietary fibre, reduce fat intake, particularly saturated fat

- Possible type 2 diabetes
- FPG ≥ 7.0 mmol/l or Hba1c ≥ 48 mmol/mol (6.5%)
- Carry out a further blood test if asymptomatic, according to national quality specifications, to confirm or reject the presence of diabetes

- No diabetes
- Offer an intensive lifestyle change programme

- Diabetes
- Enter diabetes management pathway

Reassess weight and BMI and offer a blood test at least once a year

BMI = body mass index; FPG = fasting plasma glucose; Hba1c = glycated haemoglobin

Preventing type 2 diabetes: risk identification and interventions for individuals at high risk

Issued: July 2012

NICE public health guidance 38
guidance.nice.org.uk/ph38
The effect of the ADA and FDA guidance

ADA/APA Consensus Statement

FDA warning letter/campaign

Percentage of patients receiving glucose screening

Any
Baseline

Barriers to screening

- Lack of clarity about whose responsibility it is
- Lack of understanding about what should be measured and when
- Lack of confidence in interpreting results
- Lack of access to necessary equipment

Preventing Diabetes
Risk factors for Type 2 diabetes

- Family History
- Birth weight
- Ethnicity
- Age

- Obesity
- Physical Inactivity
- Diet
Exercise & Type 2 diabetes

70,102 women, aged 40-65 yrs - US Nurses’ Health Study

1,419 cases of type 2 diabetes during eight years of follow-up

Risk reductions for type 2 diabetes according to quintile of total physical activity. Comparison is quintile 1, 0-2.0 MET hours, ie. <20 minutes per week

<table>
<thead>
<tr>
<th>Quintile</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET hours/week</td>
<td>2.1-4.6</td>
<td>4.7-10.4</td>
<td>10.5-21.7</td>
<td>&gt;21.8</td>
</tr>
<tr>
<td>Exercise time/week (min)</td>
<td>20-40</td>
<td>40-90</td>
<td>90-200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Adjusted risk reduction (%)</td>
<td>23</td>
<td>25</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.77</td>
<td>0.75</td>
<td>0.62</td>
<td>0.54</td>
</tr>
<tr>
<td>(0.66-0.90)</td>
<td>(0.65-0.88)</td>
<td>(0.52-0.73)</td>
<td>(0.45-0.64)</td>
<td></td>
</tr>
<tr>
<td>BMI adjusted risk reduction (%)</td>
<td>16</td>
<td>13</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.84</td>
<td>0.87</td>
<td>0.77</td>
<td>0.74</td>
</tr>
<tr>
<td>(0.72-0.97)</td>
<td>(0.75-1.02)</td>
<td>(0.65-0.91)</td>
<td>(0.62-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

JAMA 1999 282: 1433-1439
Lifestyle Interventions

- Lose weight to reach and maintain a BMI within the healthy range
- Reduce the total amount of dietary fat
- Eat less saturated fat
- Increase their consumption of wholegrains, vegetables and other foods that are high in dietary fibre
- Undertake a minimum of 150 minutes of 'moderate-intensity' physical activity per week
Lifestyle

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Follow-up, y</th>
<th>Participants, n</th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan et al., 1997 (80)</td>
<td>6</td>
<td>133</td>
<td>397</td>
<td>0.60 (0.43–0.83)</td>
<td></td>
</tr>
<tr>
<td>Tuomilehto et al., 2001 (76)</td>
<td>3.2</td>
<td>257</td>
<td>265</td>
<td>0.40 (0.26–0.61)</td>
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<tr>
<td>DPP, 2002 (36)</td>
<td>2.8</td>
<td>1082</td>
<td>1079</td>
<td>0.44 (0.38–0.50)</td>
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<tr>
<td>Kosaka et al., 2005 (38)</td>
<td>4</td>
<td>356</td>
<td>102</td>
<td>0.32 (0.11–0.96)</td>
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<tr>
<td>Ramachandran et al., 2006 (77)</td>
<td>3</td>
<td>136</td>
<td>133</td>
<td>0.62 (0.42–0.92)</td>
<td></td>
</tr>
<tr>
<td>All studies combined</td>
<td></td>
<td></td>
<td></td>
<td>0.48 (0.40–0.58)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q = 6.104; P = 0.192$
Are lifestyle interventions possible in people with severe mental illness?
# Meta-analysis of effectiveness of weight-management interventions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.59.1 Prevention trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvarez-Jimenez 2006</td>
<td>4.1</td>
<td>3.99</td>
<td>28</td>
<td>6.98</td>
</tr>
<tr>
<td>Cordes et al 2011</td>
<td>3.4</td>
<td>4.2</td>
<td>13</td>
<td>4.5</td>
</tr>
<tr>
<td>Evans 2005</td>
<td>2</td>
<td>3.6</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Littrell 2003</td>
<td>0.81</td>
<td>8.97</td>
<td>35</td>
<td>7.17</td>
</tr>
<tr>
<td>Polin 2007</td>
<td>84.4</td>
<td>18.2</td>
<td>59</td>
<td>88.8</td>
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<tr>
<td>Scocco 2005</td>
<td>0.99</td>
<td>3.34</td>
<td>10</td>
<td>2.96</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>168</td>
<td>156</td>
<td>36.6%</td>
<td>3.23</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.87, df = 5 (P = 0.43); I^2 = 0%
Test for overall effect: Z = 5.35 (P < 0.00001)

<table>
<thead>
<tr>
<th>1.59.2 Intervention trials</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Brar 2005</td>
<td>-2</td>
<td>3.79</td>
<td>34</td>
<td>-1.1</td>
<td>3.11</td>
<td>37</td>
<td>12.4%</td>
<td>-0.90 [-2.52, 0.72]</td>
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<tr>
<td>Khazaal 2007</td>
<td>88</td>
<td>14.9</td>
<td>31</td>
<td>83.5</td>
<td>17.2</td>
<td>30</td>
<td>1.2%</td>
<td>4.50 [-3.59, 12.59]</td>
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<tr>
<td>Kwon 2006</td>
<td>-3.94</td>
<td>3.63</td>
<td>29</td>
<td>-1.48</td>
<td>1.88</td>
<td>14</td>
<td>12.2%</td>
<td>-2.46 [-4.11, -0.81]</td>
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<tr>
<td>Mauri 2008</td>
<td>-3.6</td>
<td>2.6</td>
<td>15</td>
<td>0.2</td>
<td>2.9</td>
<td>18</td>
<td>10.9%</td>
<td>-3.80 [-5.68, -1.92]</td>
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</tr>
<tr>
<td>McKibbin 2006</td>
<td>98.5213</td>
<td>21.228</td>
<td>28</td>
<td>99.2924</td>
<td>16.919</td>
<td>29</td>
<td>0.8%</td>
<td>-0.77 [-10.76, 9.22]</td>
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<tr>
<td>Weber 2006</td>
<td>84.1848</td>
<td>6.54236</td>
<td>8</td>
<td>90.4667</td>
<td>7.35393</td>
<td>7</td>
<td>1.5%</td>
<td>-6.28 [-13.37, 0.81]</td>
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</tr>
<tr>
<td>Wu 2007</td>
<td>-4.2</td>
<td>4.4</td>
<td>28</td>
<td>1</td>
<td>3.4</td>
<td>25</td>
<td>9.8%</td>
<td>-5.20 [-7.31, -3.09]</td>
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</tr>
<tr>
<td>Wu 2008</td>
<td>63.4</td>
<td>2.6</td>
<td>32</td>
<td>67.2</td>
<td>2.6</td>
<td>32</td>
<td>14.5%</td>
<td>-3.80 [-5.07, -2.53]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>205</td>
<td>192</td>
<td>63.4%</td>
<td>-3.04</td>
<td>[-4.39, -1.68]</td>
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</tbody>
</table>

Heterogeneity: Tau^2 = 1.82; Chi^2 = 17.54, df = 7 (P = 0.01); I^2 = 60%
Test for overall effect: Z = 4.40 (P < 0.00001)

**Total (95% CI)**

<p>| | | | | | | | | | |</p>
<table>
<thead>
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<td></td>
</tr>
<tr>
<td></td>
<td>373</td>
<td>348</td>
<td>100.0%</td>
<td>-3.12</td>
<td>[-4.03, -2.21]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 1.08; Chi^2 = 22.46, df = 13 (P = 0.05); I^2 = 42%
Test for overall effect: Z = 6.69 (P < 0.00001)
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.84), I^2 = 0%
Salford weight management clinic

Data are mean ± standard error

Years after enrolment onto programme

Holt et al J Clin Psych 2010
Facilitators for lifestyle change

- Tailored and flexible programme design
  - Practical and experiential learning
- Delivered in familiar locations
- Long-term and on-going support
  - Peers, family, friends and carers
- Dedicated, sensitive and well trained staff
- Realistic, achievable goals
- Free or low-cost activities

Diabetes Prevention Program Results

Risk Reduction
- 31% Metformin
- 58% Lifestyle
- Particularly useful in elderly & overweight

- Follow-up 2.8 yrs (1.8-4.6yrs)
Pharmacotherapy

- No licensed treatments

- Preliminary evidence that metformin may attenuate weight gain in patients taking antipsychotics
  - 10/11 studies involving 495 people receiving APDs experienced weight loss or attenuated weight gain compared with placebo

- European Associations position statement
  - “....metformin may be considered in patients with additional risk factors, such as a personal or family history of metabolic dysfunction”

Management of Diabetes
Management of diabetes

- Diabetes is a complex disease to manage
  - Medication
  - Life-style change
  - Empowerment of the patient
- Requires management by a multi-disciplinary team
  - Diabetes team
  - Psychiatric team
- Importance of treating the mental state
Should we stop the antipsychotic?

- Role of antipsychotic?
- Duration of treatment?
- Other risk factors?
- Risk of relapse?
- Benefits of treatment
Treatment of type 2 diabetes

- DPP-4 inhibitors (GLP-1 agonists)
- Incretins
- Pancreas
- Sulfonylureas (meglitinides)
- Intestine
- Liver
- Insulin
- Metformin
- Glitazones
- Adipose tissue
- Blood glucose-lowering
- Lifestyle diet, exercise
- Alpha-glucosidase inhibitors
- SGLT-2 inhibitors

Adapted from Drucker DJ et al. Lancet. 2006; 368:1696–1705.
### Initial drug monotherapy

- Efficacy (HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

### Two drug combinations*

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Sulfonylurea†</th>
<th>Thiazolidinedione</th>
<th>DPP-4 Inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (usually basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (HbA1c)</td>
<td>high</td>
<td>moderate risk</td>
<td>low</td>
<td>intermediate</td>
<td>high *</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>high</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
<td>highest *</td>
</tr>
<tr>
<td>Weight</td>
<td>gain</td>
<td>neutral</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td>Major side effect(s)</td>
<td>hypoglycemia†</td>
<td>edema, HF, fx's†</td>
<td>rare†</td>
<td>G†</td>
<td>gain</td>
</tr>
<tr>
<td>Costs</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>variable</td>
</tr>
</tbody>
</table>

*If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

### Three drug combinations

- Metformin + Sulfonylurea† + TZD or DPP-4-i or GLP-1-RA or Insulin§
- Metformin + Thiazolidinedione + SU† or DPP-4-i or GLP-1-RA or Insulin§
- Metformin + DPP-4 Inhibitor + SU† or TZD or GLP-1-RA or Insulin§
- Metformin + GLP-1 receptor agonist + SI † or TZD or DPP-4-i or GLP-1-RA

*If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

### More complex insulin strategies

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

- Insulin (multiple daily doses)
Treatment of type 2 diabetes

- DPP-4 inhibitors (✔)
- GLP-1 agonists (✔)
- Alpha-glucosidase inhibitors (✔)
- Incretins (✔)
- Metformin (X)
- Sulfonylureas (X)
- Meglitinides (✔)
- SGLT-2 inhibitors (✔)
- Lifestyle diet, exercise (✔)

Adapted from Drucker DJ et al. Lancet. 2006; 368:1696–1705.
The Need for Integrated Care
Over-shadowing

- HCPs focus solely on their mental disorder and fail to take note of physical health needs.
  - Lead to decreased screening rates for diabetes and inferior diabetes care.

• Less likely to be examined for eye or foot complications
  – Despite more clinic visits
• Less likely to be screened for HbA$_{1c}$ or cholesterol
  – Less likely to receive a statin
• Receive less diabetes education
Conclusions

• Diabetes occurs more commonly in people with severe mental illness and has a disproportionate burden

• Screening for diabetes is needed before starting treatment, 3 months later and then annually

• Lifestyle interventions are crucial to prevent diabetes

• Management of diabetes largely follows standard treatment algorithms but requires multidisciplinary collaboration